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April 1960

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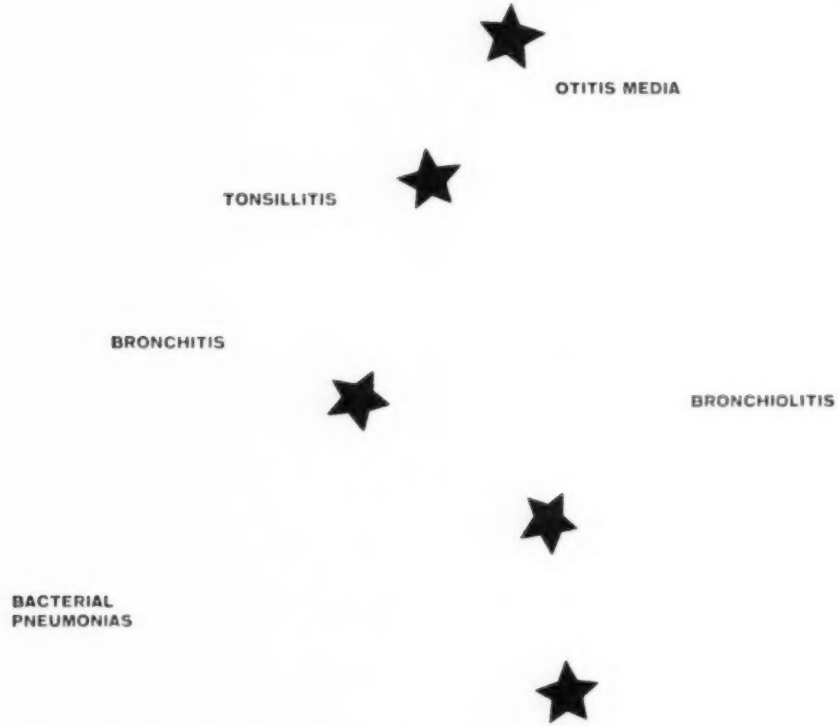

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1. Macy, I. G.; Kelly, H. J., and Sloan, R. E.: With the Consultation of the Committee on Maternal and Child Feeding of the Food and Nutrition Board, National Research Council: The Composition of Milks, National Academy of Sciences, National Research Council, Publication 254, Revised 1953.

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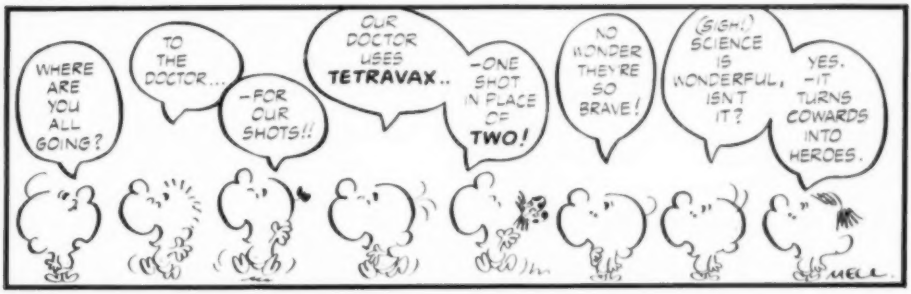
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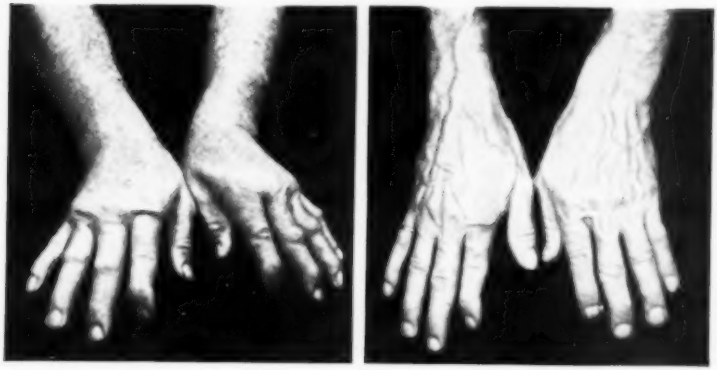

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1. Koessler, H. W.: Arch. Ped. 74:47 (Feb.) 1957.
2. Kahan, H. *et al.*: Arch. Ped. 73:125 (Apr.) 1956.
3. Editorial: J.A.M.A. 165:254 (Sept. 21) 1957.

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1. Phelps, W. M.: Arch. Pediat. 76:243 (June) 1959. 2. Spears, C. E., and Phelps, W. M.: Arch. Pediat. 76:287 (July) 1959.

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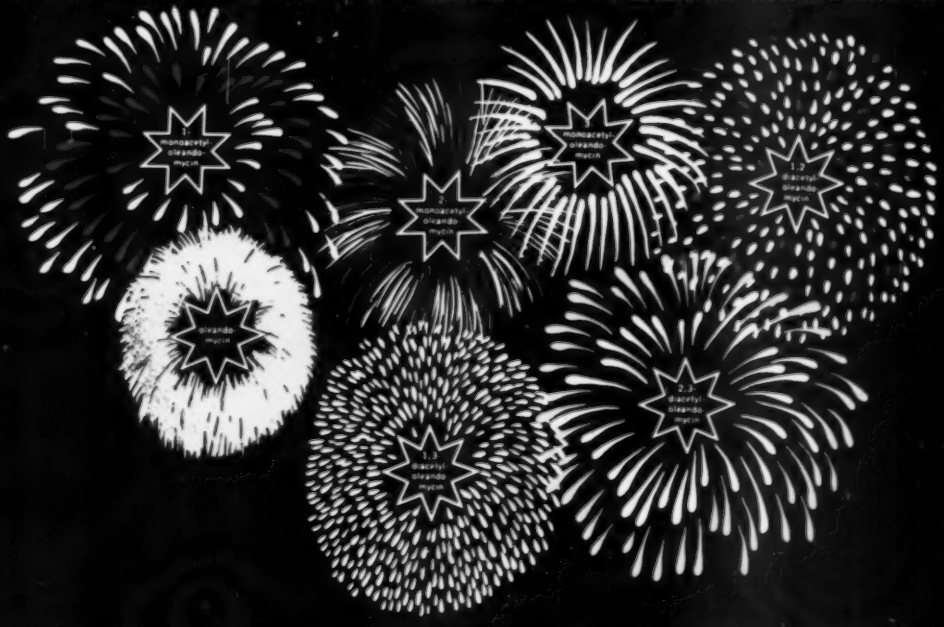

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Pediatrics in Norway

ROALD RINVIK, M.D.

Norway

Pediatrics is a young discipline in this country—young as a specialty compared to many other subgroups of medicine. The reason is obvious: a small population scattered along a rough and vast coastline and a mountain-filled land with small cities. However, the last ten years have shown great progress in the pediatric field. In 1950 our first modern pediatric wards started in Oslo and Bergen—three in number. Since then, three more have been opened in other parts of the country. Pediatrics has become one of the most important aspects of the education of the students. Postgraduate courses are given routinely. New pediatricians have begun spreading around the country taking part in the big program of preventive medicine which gradually has been developed over a period of more than 20 years with routine health examinations of mothers and infants emphasizing general hygiene and nutrition. BCG-vaccination is practised here.

Thanks to these efforts we have seen results in many respects. The mortality rate in the first year of living has reached flatteringly low figures mainly in the big cities (less than 17/1000). The figures of children with tuberculosis have rapidly been decreasing and tuberculous diseases, which two to three decades ago were rather common in children, have now, practically-speaking, disappeared. As in many other places, effective antibiotic therapy has brought the general infections under better control and fluid and transfusion therapy have become important details in the routine work at the wards.

In the field of congenital malformations, especially congenital heart disease, we still have to improve the accuracy of our diagnosis and get far more experience in the technical details of surgical treatment, anesthesia and postoperative care. Many important allergic disturbances should be benefited by increased knowledge of these conditions. Improvement can be made in the prevention of accidents. Lastly, the greatest future challenge to the pediatrician is probably the mentally disturbed child of whom there are increasing numbers.

EDITOR'S NOTE: Dr. Rinvik's observations of the remarkable pediatric progress made in Norway during the past ten years, is especially interesting for its application to practice under population-scattered, small-city, and other difficulties. (Dr. Rinvik is a member of Archive's Editorial Board.)

Children's Hospital, Oslo, Norway

Some Experimental and Clinical Studies on the Causes of Congenital Clefts of the Palate and of the Lip

F. C. Fraser, Ph.D., M.D.*
Canada

This paper will review briefly studies on the experimental production of congenital cleft palate in mice, and on the prenatal histories of children born with congenital clefts of the lip and/or palate, carried out by the writer, his colleagues and students over the past few years. More detailed presentations of these studies will be found in previous publications.

In 1950 our interest had been attracted by the increasing number of agents, such as nutritional deficiencies (Warkany, 1945), radiation (Warkany and Schraffenberger, 1947), and hypoxia (Ingalls *et al.*, 1950), that, when applied to pregnant mammals, might lead to malformations in the offspring. Although some of the early experiments suggested that there were genetic differences in response to these environmental agents, medical thought on the subject seemed to favor the view that, since environmental factors can damage the mammalian embryo, malformations in humans were likely to be determined largely by environmental factors. Our genetic bias prompted us, on the other hand, to think that even when an environmental agent was implicated, the constitution of the organism might be important in deciding how the embryo would respond to the agent. This led us to plan an experiment where an environmental teratogen would be applied to different inbred strains of mice, to see if there would be strain differences in the frequency or type of defect. At this point, Dr. Hamilton Baxter kindly supplied us with some cortisone, and we found that it caused congenital clefts of the secondary palate when injected into preg-

* Department of Genetics, McGill University, and Department of Medical Genetics, The Montreal Children's Hospital.
Resume of The First Well Born Foundation Lecture, St. Luke's Hospital, New York City, April 2, 1959. Submitted by Well Born Foundation for publication.
Financial support from the National Research Council of Canada, the Federal-Provincial Public Health Grants, and the United States Public Health Service, is gratefully acknowledged.

nant mice (Baxter and Fraser, 1950; Fraser and Fainstat, 1951). This solved the problem of what teratogen we would choose for our experiment.

EFFECT OF DOSE

As one might expect, the quantity of cortisone that produced the highest frequencies of cleft palate also reduced the size of the litter, showing that some embryos were being killed by the treatment, and resorbed. Somewhat higher doses would cause resorption of the whole litter, and it seems a general rule that the teratogenic dose of an agent is fairly close to the dose that will kill the embryo. On the other hand, some agents that will cause death of the embryo have not yet been shown to be teratogenic—e.g. hemorrhagic anemia (Wilson, 1954; Clark, 1956). Is this because the proper dose and/or stage was not tested, or because some features of the embryonic system are so sensitive that they cannot be altered, even slightly, without killing the embryo, or is it because the processes of morphogenesis are so resistant to some noxious agents that the teratogenic dose is higher than the lethal dose?

EFFECT OF GESTATIONAL STAGE

The stage at which treatment was begun also influenced the frequency of induced cleft palates. The most effective time, using a single dose, appeared to be about 12 days after conception, the palate normally closing about 3 days later. It seems clear that the "critical period" during which the palate is susceptible to interference by cortisone is quite a long one, and that it begins several days before the palate closes. This may remind us of the danger of trying to deduce, from the time that an error in morphogenesis occurs, the embryonic stage at which a causal factor acted. For instance, one should not reason that, since most of the errors in the development of the Mongolian idiot occur about 6 to 8 weeks after conception, the cause of the errors in development must have happened then (Warkany, 1957).

EFFECT OF GENETIC CONSTITUTION

After we had established an effective dose and time of treatment, it soon became clear that our prediction about the importance of the genetic constitution was confirmed. Under the same conditions of treatment, 100% of the A/Jax mouse embryos had cleft palate, as compared with only 17% of the C57BL offspring. Treatment of crosses between the two strains, and of backcrosses to the A/Jax

strain, showed that the genetic basis for the strain difference is not simple. Several genes are involved, and the final result depends on both the mother's and the embryo's genotype (Kalter, 1954).

NORMAL PALATE CLOSURE

Wondering about how the cortisone interferes with closure of the palate made us curious about how the palate normally closes. A series of observations on both fixed and living embryos showed that the palatine shelves, which before closure hang down on either side of the tongue, approach each other in the mid-line by a fairly rapid rearrangement of themselves. It appears that a force progressively builds up in the shelves, which at a given time causes them to overcome the resistance of the intervening tongue and bulge out towards each other over the tongue, with concurrent retraction of the portions of the shelves hanging ventrally. There does not seem to be any active growth involved, but a rather sudden reorientation (Walker and Fraser, 1956). It is interesting that this process begins earlier in the C57BL (cortisone resistant) embryos than in the A/Jax embryos, and earlier in the C57BL X A/Jax hybrids than in the more susceptible A/Jax C57BL hybrids (Trasler and Fraser, 1958). It would seem that the earlier beginning of palate closure is a reflection of the "strength", or efficiency, with which the shelf force is building up, and that the "stronger" shelf force is more resistant to the effects of cortisone.

THE EFFECT OF CORTISONE

Observations on cortisone-treated embryos showed that cortisone delays the process of shelf movement from the vertical to the horizontal position. If the delay is great enough, by the time the shelves reach the horizontal position growth of the head has carried them so far apart that they are unable to meet and fuse. This appears to be the basis for the cleft palate seen at birth (Walker and Fraser, 1957).

OTHER MECHANISMS OF CLEFT PALATE PRODUCTION

During attempts to inject cortisone directly into the embryo it was discovered that merely inserting a needle into the amniotic sac and causing leakage of amniotic fluid caused cleft palate in some of the treated embryos, possibly by exposing the embryo to abnormal pressures which might increase the resistance of the tongue to the efforts of the shelves to push it out of the way (Walker and Fraser, 1957). Even injecting a small amount of fluid into the

uterine cavity outside the amnion can cause the embryos to have cleft palate, but the mechanism involved here is still obscure (Trasler, 1958). Evidence from other laboratories suggests still other mechanisms by which cleft palate can be induced—for instance, there is a recessive gene in the mouse that makes the palate shelves too narrow to meet in the midline even when they reach the horizontal position at the proper time, thus causing cleft palate (Fitch, 1957).

In short, normal palate closure involves the proper coordination of many interacting processes, each of which is influenced by genetic and environmental factors, and each of which can cause failure of closure if it goes wrong. It would seem, then, that there are many causes of cleft palate. Perhaps the surprising thing is that the palate manages to close successfully so often!

RELEVANCE OF EXPERIMENTAL STUDIES TO HUMAN MALFORMATIONS

When an agent is found to be teratogenic in animals, the question naturally arises as to whether it may be a cause of human malformations. The question is a lot easier to ask than to answer. It cannot be answered reliably by evidence from scattered case-reports of children born with a malformation, found in retrospect to have been exposed to the agent. In such cases we cannot distinguish cause from coincidence. There are, for instance, a few reports of congenital cleft palate occurring in babies born to mothers treated with cortisone during pregnancy (Harris and Ross, 1956; Doig and Coltman, 1956). But we do not know how many women treated with cortisone during pregnancy had babies *without* cleft palate, and so we do not know the frequency of cleft palate in offspring of cortisone-treated pregnancies.

There are two main ways to get more reliable information about the problem. By the *prospective* approach a group of women given cortisone therapy during pregnancy would be followed, and the frequency of malformations in their children would be compared with the frequency in a comparable population of children from untreated mothers. This is tedious and technically difficult, but is the only way to get good information on the probability of an affected child following treatment.

By the *retrospective* approach, mothers of malformed children would be questioned as to whether they had had cortisone during

pregnancy, and the frequency of cortisone-treated mothers would be compared with that in a comparable group of mothers of non-malformed children. The trouble is getting a comparable control group. For one thing, mothers of malformed children are more likely to recall unusual details of their pregnancy than mothers of non-malformed children, and this is a factor that is extremely difficult to control.

A case in point is a recent study purporting to show that maternal emotional stress during pregnancy was a cause of cleft palate in the resulting babies (Strean and Peer, 1956). Mothers of children with "cleft palate or harelip" were questioned as to the occurrence of stressful situations during pregnancy. As a control the same women were asked whether such events occurred during their pregnancies that had given rise to unaffected babies. The frequency of reported stressful events was much higher in the pregnancies giving rise to the malformed babies than in the "control" pregnancies. In our series of children with cleft lip and palate a difference in the same direction was found (21% vs. 8%). At first sight this might appear to be evidence that maternal stress is teratogenic. However, we also did a control series where the patient had a disease such as albinism or hemophilia, clearly caused by genes and not due to maternal stress. These control patients had a frequency of maternal stress during pregnancy similar to that of the cleft lip and palate patients (18%), and their siblings had a much lower frequency (12%), similar to the frequency in the siblings of the cleft lip and palate series. We want to collect more data before committing ourselves on this point, but if our future results remain similar to the present ones, they would suggest that much, if not all of the difference between the patients and their siblings is due to maternal memory bias, rather than any causal association of emotional stress with malformations.

We know from family studies that cleft lip and palate show a familial distribution (Fraser, 1955; and many others). The evidence from twins suggests that the familial tendency reflects a genetic predisposition to the condition (Metrakos *et al.*, 1958). On the other hand, the fact that in 60% of one-egg twins in which at least one has a cleft lip, the other is unaffected shows that intrauterine variables are important too. These and other considerations have led to the suggestion that the genetic predisposition may make the embryo react in a particular way to rather minor environmental differences (Fraser, 1959). If so, searches for prenatal environ-

mental teratogens in humans are likely to be unrewarding (as they have been so far), and the greatest progress may come from studies of the embryos themselves to find out, in biochemical terms, what the genes are doing to make them so sensitive to their environment.

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Observations on Ariboflavinosis and Kwashiorkor in Sicily

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The recognition of conditions caused by vitamin B_2 deficiency was made possible by studies on human pellagra and especially by the identification of lactoflavin[1].

Following observations of Landor and Pallister[2] who had recognized in pellagra certain symptoms due to the deficiency of some factor different from the antipellagra one, Sebrell and Butler[3,4] kept 18 women on a pellagra-producing diet. The daily riboflavin intake was 0,5 mg. In 10 of them cheilosis was observed between the 80th and the 140th day. At first it manifested itself by an increased pallor of the lips, then as it progressed maceration of the epithelium was observed with formation of fissures, crusts and even in some points noticeable loss of mucosa. Evident signs of desquamation on an erythematous background affecting the naso-labial sulcus, the nasal alae and vestibula and the ears were added to the cheilosis. These lesions were not affected by antipellagra treatment with nicotinic acid, but they responded well to the administration of riboflavin

Of the remaining 8 women, 4 treated with riboflavin starting on the 130th day showed no cheilosis, while 4 not receiving riboflavin, showed late cheilosis. From these experimental observations, it was deduced that riboflavin deficiency could determine morbid conditions in man.

Later on, spontaneous cases of the disease were reported by Oden J. W., Oden, L. H. and Sebrell[5] among the rural population of Georgia. Three subjects treated with 5 mg. lactoflavin were cured in a few days.

There followed many other observations, reported by Anglo-Saxon authors (Spies et al.,[6] Bean and Spies,[7] Sydenstricker et al.[8] and others).

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In Europe, Meulengracht and Bichel[9] regarded as hypo-riboflavinosis the syndrome already described by Plummer and Vinson consisting of cheilosis, dysphagia, achylia gastrica and hypochromic anaemia. They noted that this syndrome was favourably influenced by the administration of riboflavin. Some cases of ariboflavinosis have been recorded in the Italian literature (Bassi and Bassi,[10] Frontali,[11,12] Berardi,[13] Bacchetta,[14] Boi,[15] Porcelli[16]). As these clinical studies appeared in the literature, the need was felt for a more solid experimental basis.

We can infer from the research on animals and human beings that a riboflavin deficient diet brings on peculiar changes in rats causing a delay in growth, conjunctivitis together with a welding of the eyelids, hair loss, stomatitis, oedema, sore ears and muzzle, with serum encrustations (Goldberger & Lillie,[17] Purpura and La Grutta[18]). In dogs, ariboflavinosis brings about: stiffness, dry dermatitis with desquamation, spastic paresis, ataxia and bradypnea (Sebrell[19]). Rats (Purpura and La Grutta[18]), dogs (Sabrell and Onstott[19]) and pigs (Miller and Co[20]) show steatosis of the liver. Following the observations of Sebrell and Butler, studies have been made on man to ascertain what is the daily quantity of riboflavin necessary for a normal state of health, and to control the manifestations caused by food lacking such factor.

The most recent research has brought to light much about the elements of the vitamin B complex and we have more exact data on the riboflavin content of different foods. On the other hand, during recent investigations, the balance existing between the quantity of riboflavin and the total amount of food has been rightly taken into consideration.

From the careful research of Horwitt et al.[21] who gave 0,5-0,6 mgr. "pro die" of the vitamin to adults of stationary weight with the diet having an energetic value of 2200 calories, we infer that the onset of the lesions due to a partial deficiency of the vitamin B_2 comes after a period of four months at least.

The patients show horizontal labial rhagades, vertical nose labial rhagades, perianal rhagades and more frequently scrotal dermatitis (redness, oozing and desquamation) adjoining the thighs. The need for sedentary adults with a diet having an energetic value of 2200 calories was of 1, 1-1,6 mgr. (Horwitt et all.[22]). Selma E. Snydermann et al.[23] found that 0,4 mgr. "pro die" of vitamin B_2 in infants prevents the onset of clinical signs of deficiency.

In this children's hospital the cases of ariboflavinosis are not unusual. They have been considered from the biological clinical and histological point of view. From the clinical point of view they show the following symptoms: 1) *Cheilosis*. It manifests itself especially by the presence of short and thin horizontal fissures at the corners of the mouth, sometimes bleeding and surrounded by dry skin or presenting a seborrhoeic aspect, but without signs of inflammation clinically observable. There is generally one fissure at each side and they are seldom more numerous. They are easily recognizable and we have also observed them in women belonging to economically poor families whose diet contained scarce amounts of animal proteins. The presence of vertical fissures associated with tumefaction of the lips was rare. Cheilosis responded to treatment with vitamin B_2. 2) Scrotal, preputial, vulvar and perineal erythema has been frequently observed (*22* subjects) and is characterised by thickening of the epidermis which is sometimes seborrhoeic and is continued in the depths of the scrotal folds; it has a cyclamen red or magenta red colour starting at the raphe and prepuce and extending to the origin of the thighs.

In girls the skin of the "labia majora" is reddened and sometimes seborrhoeic, while the mucosa tends to acquire a magenta red or cyclamen colour. The anal orifice is surrounded by a halo of reddish skin which appears independently from diarrhoea. Later on the areas of erythematous skin become brownish in colour with subsequent desquamation of thin, broad lamellae, while the epidermis resumes its normal characteristics, assuming a red colour and a normal degree of humidity.

Besides these symptoms we may also enumerate others already described by Sebrell and Butler[3,4] for riboflavin deficiency, in other words, alterations affecting the mouth, as well as the angular fissures, rhagades, already mentioned, a particular coloration of the labial mucosa, is often encountered, assumes magenta red or cyclamen shades. This aspect is easily recognizable owing also to the simultaneous presence of the angular rhagades and in contrast with the pallor of the surrounding skin. Examinations of the oral cavity reveals a similar coloration and also the tongue mucosa is often still redder and appears thinned and dry, with conspicuous papillae, or more or less smooth, presenting at times longitudinal grooves.

The soft palate and pharynx (*3* patients) show also redness and dryness and this offers an explanation for the dysphagia which is found in the same subjects.

In none of our cases did simple inspection reveal the presence of conjunctival alterations reported by the first observers, previously confirmed in one case of Stern,[24] and consisting essentially of festooned circumcorneal hyperaemia. In 9 cases hyperemia of the bulbar conjunctiva was more or less evident and disappeared after treatment with vitamin B_2 or the vitamin B complex. However, the coexistence of a certain dryness of the ocular bulb and the appearance of keratomalacia in three cases led us to believe that such manifestations might be due, at least in some cases, to the simultaneous deficiency of vitamin A.

Moreover, Gordon,[25] at the XVth International Congress of Opthalmology, has recently denied that ariboflavinosis is capable of giving rise to circumcorneal vascularisation.

So far, according to the contributions and studies on the subject, the symptomatology examined may be regarded as due to vitamin B_2 deficiency. However in the course of our research we were able to observe other morbid manifestations[26,39].

That these manifestations are part of the clinical picture of ariboflavinosis is shown by the fact that they respond to specific vitamin treatment.

They consist in the very frequent finding of extremely thin *supra- and retro-auricular rhagades affecting the epidermis, seldom reaching the dermis* and moreover bleeding, on a cyclamen-pink background, varying in length from about half to one centimeter, surrounded by seborrhoeic epidermis and localised in the supra-auricular or retroauricular sulci. Sometimes it was possible to observe the initial stage, which may be described as a seborrhoeic condition of a linear area of skin, which assumed a cyclamen-pink colour and in the center of which rhagades came to be formed at a later stage.

From the biochemical point of view, it has been observed in this laboratory (G. Russo)[40,41], that those patients after a single injection of riboflavin eliminate a small amount of riboflavin while they retain the major part of vitamin injected.

As to the morphological aspect, the histological alterations of the liver have an unusual importance. They can be easily shown in during life by biopsy. In this clinic biopsies were made by Albeggiani[42] which showed constant widespread parenchymatosis, albuminous degeneration, and steatosis generally in small and medium droplets with either a perilobular or medium zonal localization.

Besides these patients we observed a certain number who showed not only the symptoms of deficiency of vitamin B_2 above mentioned, but also many others, so that the biochemical, anatomical and clinical picture corresponded to that particular syndrome known generally in various countries under different names (Kwashiorkor, diboba, maladie oedemateuse du sevrage, infantile pellagra, malignant malnutrition (Williams,[43] Davies,[44] Dean,[45] Adam,[46] Trowell, Davies and Dean,[47] Achar and Benjamin,[48] Stransky and Dauis-Lawas,[49] Brock ed Autret,[50] Autret e Behar[51]) but more commonly known as Kwashiorkor.

As it is known the symptoms are:

1—denutrition; 2—edema; 3—apathy; 4—alteration of the skin (erythemas, split fissures, desquamation, dyskeratosis) and of the hair (fragility, dryness, depigmentation to acromotrichia); 5—hypodisprotidemia; 6—hepatic steatosis; 7—simple or severe anaemia, at times hyper-or hypochromic with megaloblastosis in the bone marrow (in the hyperchromic cases) with particular alterations of the granuloblasts.

Bone marrow examinations show an increase in the differential count of the granuloqoietic cells, generally very immature (granuloblastic hyperanaplasia). Among them a certain number of very large elements may be observed, with hypersegmentation of the nucleus in the polymorphonuclears. The first finding is more common in myelocytes and promyelocytes but is also evident in myeloblast and often the nuclei show histioid features. 8—Marked decrease of the pancreatic enzymes contained in the duodenal juice (trypsin, steapsin, amylase); 9—mild steatorrhea; 10—altered processes of hemocoagulation; 11—Signs of deficiency of vitamin A (Keratomalacia) B_1, B_{12}, PP, C and hypoelectrolytemia (Kalium).

In this Hospital my coworkers and I[20, 42, 52, 62] have closely studied such patients from the clinical, histological and biological point of view.

We made the following observations on the etiopathogenesis:

(1) That the pre-existence of an infectious enteritis is to be found almost constantly.

(2) An animal protein hypoalimentation is frequent in infants.

(3) Mothers of the sick children frequently have an alimentary deficiency during pregnancy and nursing so that they take in a very small quantity of animal proteins and fat and very little calcium, iron and vitamins (B_1, B_2).

The etiophathogenesis in our patients suffering from Kwashiorkor is the result of the above mentioned factors. The disease is determined by the action of the infectious diarrohea in individuals who have a deficiency of proteins and of vitamins.

However there are patients whose previous alimentation at the onset of Kwashiorkor was normal (breast feeding, powdered milk). These latter cases are not the result of an alimentary protein deficiency, but are due to the diarroheic enteritis which inhibits the absorption of aminoacids and vitamins; especially methionine and riboflavin.

While the prognosis for a simple ariboflavinosis is favourable; the prognosis for Kwashiorkor is serious.

Our patients were treated with transfusions of plasma or whole blood, vitamin injections or hepatic extracts, drugs which cure the infectious enteritis and an alimentation rather rich in animal proteins.

Since 1950 we started using chlortetracycline (aureomycin) (50 mg. "per Kg." daily) for the treatment of Kwashiorkor and simple ariboflavinosis. The results have been good. We may also add that sometimes the effect was even surprising, and caused rapid recovery in infants whose conditions could be regarded as hopeless owing to the gravity of the clinical syndrome and the inefficacy of other treatments (blood transfusions venous infusions, vitamin B_{12}, etc.)

There was first an improvement in the general conditions, awakening of the mental faculties and of the appetite, renewed vivacity and circulatory recovery, which were accompanied or followed by regression of the clinical signs of the deficiency and particularly of the erythema. The weight curve, apart from edema, rose rapidly (with as much as 70 gr. daily increase); the blood serum proteins tended toward a normal level.

At the same time blood formation improved, diarrhoea diminished and soon disappeared and the feces showed an ointment-like dense consistency and a golden yellow color. Bacterial examination showed the disappearance of bacterium coli and the persistence of proteus.

From the beginning, the explanation of the mechanism of action of aureomycin seemed rather difficult, and even today we do not think we know it for certain.

Nor is it very likely that the rapid improvement might be attributed to the disappearance of diarrhoea, since there was simultaneously a notable reduction in the intestinal bacterial flora, and the amount of riboflavin and other vitamins taken in with the food during the treatment period was so small as not have a prompt curative effect.

Our observations on the favourable effects determined by the treatment with chlortetracycline (aureomycin) in B_2 deficiency and in Kwashiorkor, which were remarkable in a certain number of patients, were confirmed by Charmot et al.;[63] in North Africa they treated with aureomycin some infants suffering from Kwashiorkor. More recently R. A. Lewis et al.[64] in India treated 4 patients with chlortetracycline giving small amounts (25 mgr. a day for two months). They noticed a more rapid improvement in the patients so treated in comparison with those who had undergone the usual treatment both in the cases of anaemia and hypoproteinaemia.

CONCLUSIONS

1. There are in Sicily cases of ariboflavinosis, very frequently having other vitamin deficiencies (A, B_1, B_2, C, PP) and mineral deficiency (potassium).

2. There are also evident cases of Kwashiorkor.

3. Of pathogenic importance to both is a previous infectious diarrhoeic enteritis causing the malabsorption of aminoacids and vitamins.

4. Such diarrhoea may make worse an alimentary protein deficiency condition while can show a state already existing and not yet apparent of alimentary deficiency (proteins and vitamins).

5. Chlortetracycline, introduced by us in the treatment of both diseases since 1950, has given favorable results, along with transfusions of whole blood or plasma, and injection of the deficient vitamins and suitable alimentation.

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Cor Biloculare-Report of 3 Cases

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Cor biloculare is among the rarest of congenital cardiac lesions. There are many reports in the literature that present various aspects of this condition and cover the field well. These three cases are presented to: 1) Increase the awareness of the physician to the possibility that a congenital heart defect might be cor biloculare. 2) Point up the fact that the history, physical examination, and diagnostic aids are inadequate to make a definite diagnosis of this condition. 3) Re-emphasize the rarity of this condition.

CASE REPORTS

Case 1. J. B., a white infant male was born at 4:00 A.M. August 29, 1950. He weighed 9 pounds, 11 ounces at birth. He had been cyanotic and dyspneic since birth. Auscultation early in life revealed decreased breath sounds that later cleared. No murmurs were heard. At 1:00 P.M. August 29, 1950 his temperature was 37° C. At this time diffuse grayish-blue cyanosis of the face and extremities was noted. Increased respiratory rate and diaphragmatic retractions were present. The chest was hyperresonant more marked on the left. At this time it was felt that the infant had disseminated and possibly massive atelectasis. X-ray of chest on August 29, 1950 seemed to reveal atelectasis. Child was given oxygen, placed in Trendelenburg position and given prophylactic penicillin. The dusky cyanosis and hyperpnea continued on August 30, 1950. The child refused his feedings. The left lung field seemed more involved than the right by auscultation. It was felt that the child had atelectasis complicated by pneumonia. On August 30, 1950 the Hemoglobin Concentration was 17.5 Gm. per 100 cc. White blood cell count was 16,100/cubic millimeter; Lymphocytes, 29%; Monocytes, 1%; Eosinophils, 4%; Stabs, 16%; Juveniles, 1%; Polymorphonuclear leukocytes, 49%. On August 31, 1950 another chest X-ray was done and the X-ray seemed to reveal clearing of

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the lung fields. The cardiac shadow was dilated with increased diameter at the base with an appearance suggestive of congenital heart disease. The types of heart disease considered were two-chambered heart; coarctation of the aorta with closing patent ductus arteriosus and tetralogy of Fallot. On August 31, 1950 at 7:10 P.M. the infant expired. Cyanosis, hyperpnea, and diaphragmatic breathing had remained until his exodus. Terminally, he had an enlarged liver felt 3 finger-breadths below the right costal margin. Pathologic description of the heart:

The heart presents a definite abnormality. There is only one ventricle from which only one great artery is seen emerging. A right auricle is present which is slightly larger than normal. The inferior and superior vena cavae drain into this auricle. The left auricle is represented by a vestigal remnant which is non-functioning. The right and left pulmonary arteries are branches of the common trunk leaving from the single ventricle. The arch of the large vessel is of average size and has the three branches leaving immediately at the mid-portion of the arch: the innominate, the left carotid, and the left subclavian arteries. The proximal aorta is a fibrous cord. The remainder of the aorta is not remarkable. Hence, in summary, this heart is a two-chambered heart composed of a right auricle and a common ventricle. There is a truncus arteriosus present from which the two pulmonary arteries are derived.

Case 2. E.D.A., a white male was born December 22, 1958 at 11:50 A.M. He weighed 6 pounds, 13½ ounces at birth. When seen at first there was no evidence of disease. At 5:30 P.M. the pediatric resident had been called to examine the infant because of rapid, shallow, labored respirations. (This was on December 23, 1958). He was cyanotic and appeared flaccid. The temperature was normal. Auscultation of the heart revealed rapid sinus rhythm with no thrills or murmurs. Anterior fontanel was not tense. The examining physician thought that this baby had hyaline membrane disease or pneumonia. An X-ray of the chest and white blood cell count with differential were ordered. Oxygen therapy and penicillin were given. The chest X-ray was difficult to interpret due to technical reasons but the radiologist felt that the film was suggestive of hyaline membrane disease. (It is important to note that this infant was not premature and that he was not delivered by means of a cesarean section.) When seen at 8:45 P.M. 12/23/1958 he had subcostal retractions. He was still cyanotic when out of oxygen. Auscultation of the heart revealed no murmurs. There was

questionable enlargement of the liver. The infant's feet were cold. Feeling that septicemia might be present a blood culture was done. Blood electrolyte studies were also done. Electrolytes were: Sodium 146 milliequivalents per liter; Potassium 6.2 milliequivalents per liter; Chlorides, 100 milliequivalents per liter. Hemoglobin concentration on 12/23/1958 was 13.5 Gm./100 c.c. and the hematocrit was 44 per cent. The white blood cell count was 13,300 per cubic millimeter. Lymphs were 37%, Monos, 5% and Eosinophils 3%. The remainder of the differential was not recorded. There were 15 nucleated red blood cells per 100 white blood cells.

On December 24, 1958 at 12:50 A.M. the color was better and patient seemed less cyanotic. The respiratory rate was still rapid (64/minute) and the apical pulse was 148/minute. The infant was started on blood and broad spectrum antibiotics. At 1:00 P.M. the subcutaneous tissue of the cheeks, back, buttocks, outer aspect of the thighs and upper aspect of the abdomen felt very firm to the touch. He had passed less than 15 c.c. of urine in 20 hours. He was catheterized at 4:30 P.M. 12/24/1958 and no urine was obtained. Hemogram on December 24, 1958 was as follows: Hemoglobin concentration 16.8 Gm./100 c.c. White blood cell count 33,500 per cubic millimeter. Lymphocytes 21%; Monocytes, 9%; Myelocytes, 1%; Juveniles, 1%; Stabs, 6%; Polymorphonuclear leucocytes, 61%.

At 8:30 A.M. on December 24, 1958 the child expired. Pathologic examination of the heart: The heart weighs 22 grams. The epicardial surface is smooth and glistening. The apex of the heart seems to be very broad. On opening the heart it is found to have only two chambers, one large atrium and one large ventricle with no evidence of any attempt at septum formation in the auricle, although in the ventricle there is some slight attempt at a septal formation. A very large truncus arteriosus arises from the common ventricle. There is a valve between the atrium and the ventricle which measures 6.5 cm. in circumference. There is a valve at the truncus which measures 2.5 cm. in diameter. Just above this valve there are two pulmonary arteries coming off from opposite sides of the truncus. Just above the origin of these vessels there is another valve in the truncus which measures 1.5 cm. in circumference. This is the aortic valve and beyond this is the arch of the aorta and from the arch the three vessels, the right common carotid, the left common carotid and left subclavian arteries arise.

Case 3. V. S., a Negro female was born at 12:10 A.M. on June

8, 1959. She was not cyanotic at birth and appeared normal. She weighed 6 pounds at birth. She did well until June 10, 1959. It was noted at 2:00 P.M. that she did not nurse well. Cyanosis of the extremities was noted. She appeared pale. Her respiratory rate was rapid. Later that afternoon circumoral cyanosis was noted. That evening the child seemed to be somewhat rigid. On June 11, 1959 she had a poor Moro reflex. She nursed poorly and tired easily when nursing. At 12:45 P.M. on June 11, 1959 she had grunting type respirations with retractions and appeared somewhat listless. At 2:00 P.M. her temperature was 96 F. Her chest was clear to auscultation. She cried if disturbed and felt cold. Hemoglobin concentration on June 11, 1959 was 19.8 Gm/100 c.c. The child was placed in an incubator and oxygen given beginning at 12:45 P.M. June 11, 1959. It was felt that this child had brain damage or intracranial hemorrhage. At 2:20 P.M. June 11, 1959 she expired. Pathologic examination of the heart: The heart, which lies free in the pericardial sac, weighs 20 grams. It is moderately enlarged, due to dilatation, and globular in shape. On opening, no interventricular or intrauricular septum is present. A large 3 leafed valve, with chordae tendinae and papillary muscles, separates the auricle from the ventricle. One large artery, the aorta, arises from the ventricle and from this vessel the pulmonary arteries arise. The 3 leafed valve, which has the structure of an aortic valve, is unremarkable. One very thin coronary orifice is identified.

DISCUSSION

Cor biloculare was first reported by Wilson in 1798. Cor biloculare with persistent truncus arteriosus was first described by Preisz in 1890 but was first fully described by Abbott in 1936. In 1936 Abbott reported 14 cases of cor biloculare.

Cor biloculare is not usually compatible with life. Most infants with this condition die within the first few weeks. Due to adequate pulmonary circulation some patients have survived to adulthood. Nelson and Wells described a patient with cor biloculare and transposition of the great vessels who lived to be 27 years and 3 months. A patient with cor biloculare and persistent truncus arteriosus reported by Carr, Goodale, and Rockwell lived to be 36 years and 2 months.

Since this condition is so rare it is not suspected in most cases. Of the three cases reported in this paper cor biloculare was considered in only one of the cases.

There are no pathognomonic signs in this condition. In most cases cyanosis of varying degrees is present. Dyspnea is frequently present. Cyanosis and respiratory difficulty were present in the 3 cases here presented. In the first case cyanosis appeared at birth. In the second case cyanosis appeared after about 20 hours. Cyanosis appeared in the third case after about 60 hours. In each of the three cases respiratory difficulty was noted at about the same time cyanosis was detected. In some cases a systolic murmur may be heard but this does not offer much in the way of arriving at a specific diagnosis. Continuous murmurs have also been reported. A thrill was found in the patient reported by Campbell, Gardner, and Reynolds and in the patient reported by Carr, Goodale, and Rockwell. Chest X-rays may lead one to make a diagnosis of congenital heart disease but there is nothing seen to enable one to make a definite diagnosis of cor biloculare. Clubbing of the fingers does not usually occur for most patients die before this phenomenon has had time to manifest itself. It has been seen in patients above 2 or 3 years of age and in older patients. Persistent truncus arteriosus is the most common anomaly associated with cor biloculare. The first two cases presented had truncus arteriosus but no truncus was present in the third case.

In the past 10 years at Kern County General Hospital (Period ending June 30, 1959) there have been 20,943 live births and 369 stillbirths. 361 deaths have occurred in the pediatric age group (excluding newborns) and 273 autopsies were done. In the newborn period 444 deaths have occurred with 269 autopsies being done. Of the 542 patients on whom autopsies were performed (newborn and pediatric age group children) 48 had cardiac lesions. These cases were distributed as follows:

Condition	Number of newborns with this condition	Children in pediatric age group with this condition	Total
Cor biloculare	3	0	3
Fibroelastosis, endocardial	0	2	2
Congenital heart disease, unclassified	2	7	9
Cor triculare biventriculare with patent ductus arteriosus	0	1	1
Cor triloculare biatriatum with patent foramen ovale	1	2	3
Patent ductus arteriosus	12	4	16
Patent foramen ovale	0	2	2
Patent foramen ovale with patent ductus arteriosus	3	2	5
Multiple septal defects	3	2	5
Coarctation of aorta with patent foramen ovale	1	1	2
Totals	25	23	48

SUMMARY

1. Three cases are presented. Each of the patients had cyanosis and respiratory difficulty. In no case was a murmur or thrill present.

2. Cor biloculare is one of the rarest cardiac lesions.

3. There is nothing in the history, physical examination, or chest X-ray that will enable one to make an unequivocal diagnosis of this condition.

4. Cor biloculare is not usually compatible with life most of the infants dying within the first few weeks of life. In the literature one patient with cor biloculare and transposition of the great vessels lived to be 27 years and 3 months while another patient with cor biloculare and persistent truncus arteriosus lived to be 30 years and 2 months.

5. When seeing very young infants with symptoms of heart disease unless the infant has some definite indications of a specific type of heart disease (i.e. lower blood pressure in the legs than in the arms in coarctation of the aorta or the machinery murmur in patent ductus arteriosus, etc.) it would be well to at least consider this diagnostic possibility even though it is realized that cor biloculare is extremely rare. As has been forementioned it was considered in one of the cases presented in this paper.

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618 *California Avenue, Bakersfield*

Pediatric Conference . . .

THE ROOSEVELT HOSPITAL, NEW YORK

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EDMUND N. JOYNER, III, M.D., *Chief of Pediatrics, Presiding*

HEINZ F. EICHENWALD, M.D., *Associate Professor of Pediatrics Cornell University Medical College, Guest*

DR. JOYNER: In the fields of pediatrics and in medicine, I think one of the most common problems that we all see, and by far the most common infectious problems that we see, are those conditions which are caused by viruses. It's been reliably estimated that in children, 75% to 85% of all upper respiratory infections are primarily caused by viruses.

Our grandfathers who were physicians, used to call it grippe. *We* now call them viruses, or virus infections and usually get by with that. However, they do have some rather important connotations, primarily in their relation to the use of antibiotics. The viruses I'm sure have added much to the dividends of stockholders in the pharmaceutical companies, and without one bit of harm to a single virus! Antibiotics not only do no good in combatting virus infections — there is evidence that they do harm.

So that the antibiotic problem then, is primarily one of the clinician trying to determine which infection is caused by a virus and which is caused by a bacterial infection. This, in some instances, is easy. The surest way is in the presence of a wave of virus diseases producing a specific clinical entity such as, for instance, we've been going through in the last two weeks, a typical gastro-enteritis running a very definite course, with acute vomiting lasting anywhere from 12 hours — sometimes slightly shorter — up to two days with temperature running 101, 102; some upper respiratory symptoms, usually running nose, followed by diarrhea lasting two or three days; also when one hears on the telephone, that many of these cases are occurring at one time, you're reasonably sure, even on the tele-

phone, that they are caused by virus. At the present time we have no way, in an ordinary hospital laboratory, of finding out what that virus is.

It's true that we have no method at the present time of treating the virus — even if we did find out what it is — but it would be very instructive and helpful if we could correlate some of the laboratory findings on these viral diseases with the clinical symptoms and course; also if we knew exactly where virologists stand in identifying viruses of the various types. Certainly, the pandemic viral infections have been worked out very well, and very rapidly there have been developed vaccines and protection for them. But there are hundreds probably, of the ordinary viruses which we find every day, that are endemic. At the present time we have no specific method of identifying them except clinically. Another practical aspect is that we know that many of the viruses, particularly of the ECHO type, (less often I think than the adeno viruses) quite frequently will cause a rash which is not very dissimilar to that of German measles. I feel that's the reason, among lay people, why there's a great belief that German measles can occur more than once. True rubella doesn't occur more than once. It is also said that a good way to tell rubella is by the enlargement of the post-occipital nodes. It has certainly been my experience that in almost any viral infection the posterior occipital nodes are involved, so I don't think that helps us. Again, it's a total clinical picture.

In order that we might get some help from an individual who has been closely interested and has worked considerably both in the laboratory and clinically, we've asked Dr. Eichenwald to come in today and help us out a little bit — to tell us something about the laboratory methods of identifying viruses, some of the established clinical pictures of certain of the viruses. Except incidentally, I don't think he will touch too much on the measles and chickenpox ones, but the more common ones — the ones we see and have to deal with from day to day. So with this rather long introduction, I will now ask Dr. Eichenwald to take over.

DR. EICHENWALD: Thank you Dr. Joyner. It is of course impossible to discuss the many viruses which have been isolated since the introduction of practical tissue culture methods by Dr. Enders and his associates about 7 years ago. Certainly, the progress in the last five years has been so rapid that virology, like pediatrics, has broken down into a number of sub-specialities. General virologists are be-

ginning to disappear and special types of virologists are beginning to take their place: specialists in respiratory viruses, specialists in central nervous-system viruses, specialists in gastro-intestinal viruses, etc. There are people interested simply in serologic identification, people who are interested primarily in isolation of viruses (not even in their identification) and then finally, there is a group of individuals who work in some of the more abstract phases of virology, the development of immunizing vaccines, and the increase in knowledge of the nature of viruses.

I think it might be best to first limit the discussion a little bit. Because the story of the entero viruses, including the ECHO's, the Coxsackies, and the polios, is quite well known, I will try to limit myself today chiefly to the respiratory agents. As you know, the first agents to be identified in this group, were the influenza viruses.

Classical influenza, I think, is well known to all of you. Children generally have influenza in a much milder form than adults, except under conditions where there is chronic lung disease, or disease of the cardiovascular system, specifically mitral stenosis.

Influenza virus undergoes periodic antigenic variation. This is why the Asian influenza pandemic occurred. We will in the next decade get another antigenic variation and probably another epidemic. Basically, all influenza viruses fall into three groups: A, B and C. Most of the trouble recently has been due to variants of the A, the A^1, and, as the Asian flu is known, the A^2. It is not expected that this year will be a particularly heavy influenza year in New York. There will undoubtedly be some endemic cases, but epidemics will not occur in the New York area. It is estimated on fairly good evidence that the three years during which the Asian influenza virus was prevalent in this community resulted in immunity to this particular variant in more than 70% of the population of New York City. This alone would give pretty good protection against an epidemic this year. Now, there are other influenza-like viruses which have recently assumed considerable importance. I'd like to list those for you.

The ones of greatest importance are the HA-1, and the HA-2 viruses. Even during the pandemic of influenza in 1957 and 1958 at New York Hospital, we saw more children in the out-patient department who were suffering from HA-1 and HA-2 disease than we saw cases of influenza. This may have been due to the fact that

these illnesses in children were more severe, and therefore the patients came to the hospital rather than influenza patients, who generally stayed at home because the disease was so mild. We will discuss these two viruses in more detail.

The CA-virus comes by that name because of the fact that it was thought and still is thought to be associated with certain cases of croup, CA stands for "croup associated". This particular agent was isolated for the first time almost simultaneously in three different areas: Cincinnati, by Dr. Chanock, in Toronto, and also in New York City. At that time many of the patients who were seen with severe croup in these three areas, had CA virus infections. Since then, however, this virus is disappearing from the scene, and it has been isolated infrequently from patients with croup. This probably means that the CA-virus runs a cyclical epidemiologic pattern.

The term HA-1 virus stands for hemabsorption virus, type 1; HA-2 stands for hemabsorption virus, type 2. These viruses are very prevalent in the community; they are probably the most important known respiratory viruses that a pediatrician deals with. They certainly out-shine the adeno-viruses in this regard. The adeno-virus has been popularized more perhaps, but of the clinical disease that one sees, the HA viruses account for a higher proportion. The HA-1 virus generally causes an upper respiratory disease, and if it descends it tends to cause a bronchopneumonia. The HA-2 virus also causes upper respiratory disease, but it has a special propensity for producing croup, and the HA-2 virus is probably the chief known viral cause of croup in this area.

The HA-1 and HA-2 viruses are of some technical interest. They, like the influenza viruses, multiply in chick egg embryo. They multiply in monkey kidney tissue too, which as you know, is the chief tool of practicing virologists, but they do not produce very definite changes in these tissues. The effect of the virus on the tissue is not easily visible and probably because of this, the virus was missed until a very interesting technique was introduced which consisted simply of adding guinea-pig red cells to the tissue culture, and, in the presence of the virus, the guinea-pig red cells adhere to the monkey kidneys' cells.

The Sendai virus is a Japanese agent. It was once called influenza D, and is still sometimes referred to as that. It is ap-

parently a cause of some respiratory infection in that country. Its actual clinical importance is a matter of dispute. The Sendai virus in Japan apparently caused outbreaks of newborn pneumonitis and because of this, the literature of about five years ago or so referred to it as Sendai newborn pneumonitis virus. This agent is related immunologically to the CA virus, and slightly to the other agents that I have mentioned. It is also, like the CA virus, related antigenically to mumps.

The adeno-viruses are the next group to discuss. The adeno-viruses, as you will recall, date back about four years, and in this four-year period, this group has mushroomed into a collection of over 20 agents, all of whom share some antigen in common, but all of whom differ sufficiently virologically from each other, so that they can be distinguished serologically. The adeno-viruses received a great deal of public attention, but in pediatric practice, they do not appear to be important. For example, the entire group of adeno-viruses accounts for less than 3% of all febrile respiratory disease that we see in children in this area. It is true that a few cases of lower respiratory track disease, croup, etc., have been associated with an adeno-virus type 1 and 2 infection, but whether, in fact, these were the agents responsible for the disease is unknown because adeno-virus type 1 and 2 are extremely prevalent. Most children by the time they've reached age 3 or 4 have had infections with these agents. These agents tend to persist in tonsillar tissue for extremely long periods of time, but it seems certain that much infection from these agents is asymptomatic.

Type 3 adeno-virus causes an actual, distinct clinical picture, and this is the disease which has been called pharyngo-conjunctival fever. This illness is marked by a respiratory infection, with pharyngitis, frequently a dry cough, usually associated with a conjunctivitis, with pre-auricular lymph node enlargement. The conjunctivitis is quite marked; it may occur without any pharyngeal involvement in which case it's simply "pink eye" or, as some epidemics have been called, swimming-pool conjunctivitis. There is an association between adeno-virus type 3 and the epidemic form of conjunctivitis in the summer time. The adeno-virus type 3 chiefly appears to be a summer disease, and the epidemics that have been described occurred in children's camps during July and August. There have been a few others that have occurred at other times of the year, but adeno-virus type 3 is not a very prevalent agent except in these epidemics.

Adeno-viruses types 4 and 7 are of some interest because they, for some reason or other, seem to affect primarily military populations. Adeno-virus type 4, for example, has caused a great deal of difficulty at the Great Lakes Training Station of the Navy, and most recruits who come there develop a febrile, respiratory disease during the first two or three weeks of their stay. However, to find type 4 in a civilian population has proved nearly impossible. Type 7 is fairly similar. Again this causes epidemics mostly among military people. It seems to like uniforms but it does not affect, for example, student nurses, or medical students, whom one would suspect to be at least equally susceptible with the military population. Adeno-virus type 8 specifically causes a keratoconjunctivitis which is not seen very much in this country but which has been reported on the West Coast.

The other adeno-viruses are either not clearly associated with disease or have been isolated with such infrequency as not to permit any definite statement as to the pathogenic potential, or the clinical picture that they produce. Because of the popularization of the adeno-viruses, there has been an attempt by one or two pharmaceutical houses to introduce an adeno-virus vaccine. My own feeling is, while this adeno-virus vaccine, particularly for adeno-virus types 4 and 7, might be useful in the military population, there is absolutely no reason to use it in pediatrics.

There are a number of other respiratory agents. One of them is a very interesting one. That's the primary atypical pneumonia virus, which has more properties than simply causing primary atypical pneumonia. It's usually called the PAP virus, and was first described by Eaton using a system which did not involve the use of tissue cultures. At the time when Dr. Eaton described this agent, there was a great deal of skepticism as to whether he had, in fact, isolated a virus agent, or an agent that caused primary atypical pneumonia. In the last year and a half this work has been amply confirmed by the introduction of an entirely new method into virology, and this is the fluorescent antibody technique. It has been shown, by Dr. Coons at Harvard, that it is possible to label anti-bodies with a dye which when subjected to ultra-violet radiation, fluoresces. He worked out the methods for this, including the equipment which at the present time is relatively expensive. With this technique, it is possible to demonstrate the presence of antigens of any type in tissue, simply by exposing the tissue to antibody, exposing the whole works to ultraviolet light, and

looking at it under the microscope. Within this tissue one will see the fluorescing of the antigen antibody complex. What one can also do is to subject the antigen to unlabeled antibody, let's say of human source, and then to label the whole works, the antigen-antibody complex, by exposing it to a labeled anti-human gamma globulin. In other words, any antigen which is combined with any human gamma globulin will now be picked up by the anti-human gamma globulin labeled material. This is the indirect fluorescent antibody technique which has been applied with great success by Dr. Liu to show that Dr. Eaton's work was correct.

But the additional information gained from a continuation of Dr. Eaton's initial work, is that the primary atypical pneumonia virus accounted for other illnesses, and appears to be of great importance in febrile respiratory disease in young children as well as adults. This agent causes respiratory disease, with croup, acute laryngeo-trachael bronchitis, bronchiolitis, bronchopneumonia and primary atypical pneumonia. It can be shown that while the cold agglutination is perhaps a reasonably good test, this procedure is certainly not terribly specific, particularly in children, where, as you know cold agglutinants are frequently absent, even in absolutely characteristic cases of primary atypical pneumonia.

Another agent which was very popular in the newspapers and disappeared recently from public view, was the JH virus, described at Johns Hopkins. It was believed to be one of the causes for the common cold. It turns out that it is not, and that it is also probably of no great importance at the present time. An agent which is probably identical to it was described by Dr. Mogabgab at the same time and it goes under the number 2060. This is a difficult agent to deal with whose exact affinities are still unknown because of the difficulty of working with it. An agent very similar to this is DP 471.

Another agent which has a somewhat checkered career is a virus which goes under the name of CCA. This stands for "chimpanzee coryza agent". It was isolated initially from chimpanzees who developed colds when exposed to humans; the humans did not get colds when exposed to chimpanzees. It was then studied extensively by Dr. Chanock, who showed that this agent is very prevalent among infant groups, particularly infants who are hospitalized.

Now, two other agents which I might mention briefly are the U virus, described in Sweden. It is another cause of the croup

syndrome, but there has been, as far as I know, little work done with it in this country. It has not been isolated by us and I don't know what the importance of this agent might be. Another virus similar to the U virus is one of Dr. Mogabgab a COE virus, a respiratory virus of unknown affinity.

The final agent that I can recall off hand is an ECHO and this is the one ECHO virus that has been shown to cause respiratory disease. As you know, the ECHO term refers to enteric cytopathogenic human orphan viruses, and to say that an ECHO virus causes respiratory disease may be a paradox, and of course, in a way it is. ECHO viruses are classified as ECHO viruses particularly because they were initially isolated from the gut and because they have certain affinities in tissue cultures and act in a particular manner in an artificial system. Since a child will swallow most of its respiratory secretions, it is not uncommon to get respiratory viruses in the gut. Therefore, in an infant one can easily identify adeno-viruses in the stool. The ECHO 20 in children, at least, seems to cause respiratory disease and to multiply chiefly in the respiratory tract. This agent was described by Cramblett a few years ago. It causes moderately severe illness, fever, cough, sore throat, and that's about it. It's one of these non-critical diseases which one sees so much of and which without extensive laboratory work one cannot really define.

The greatest problem in virology at the present time is the expense and time required to establish an etiologic diagnosis. This is due to the fact that the monkey tissue is expensive to prepare since one has to start with monkeys to get the monkey kidney tissue, and other cells like the hela are expensive to maintain because they have to be fed and nursed along very much like premature infants.

A few years ago we had an epidemic which consisted of diarrhea and which we found out two years later was caused by ECHO 18. It took two years to identify the ECHO 18 viruses. The trouble was that we started with ECHO 1 and worked up, which was the only way to do it because when first we saw this epidemic, ECHO 18 had not yet been described, so we couldn't have started with ECHO 18 and worked down. By the time we got up to ECHO 17, the number of known agents had already increased to 25, and we kept thinking that we'd have to keep on going the rest of our lives trying to test against ECHOs which people were discovering just about

as fast as we were able to produce the anti-serum and do the neutralization tests. It turned out fortunately, that when we got to ECHO 18, we had the virus. This is also true when you identify respiratory agents. You've got to work through this whole battery of agents; you have to do various tests to classify them, and then go through the expensive immunologic tests, trying to identify the particular species to which it belongs. It is possible that with the fluorescent antibody technique this will be simplified. I don't know if this is true. This is why I think all of us turn a little bit green when a clinician arrives with 8 or 10 specimens in his hand and says: "Please, tell me what virus this is." First, this costs money; secondly, it takes a tremendous amount of time, and thirdly, if you're unlucky enough to isolate a virus, it may tie up the laboratory for the next month or so trying to identify it.

This is the reason why you have to, as clinicians, be a little bit patient with virus laboratories. It is much more difficult than bacteriology ever was; it is frightfully expensive, and is something which certainly in the foreseeable future will not become a regular clinical tool.

In the next few minutes, I'd just like to say a few brief words about a subject which I know is dear to Dr. Joyner's heart and also dear to my own, and this is the use of antibiotics in viral infections. Dr. Hope Craig Perry and I and some of our associates at the New York Hospital a few years ago, did a study which we have so far not gotten around to publishing. We saw all children that came into the pediatric emergency room or the isolation unit with respiratory infections. They were seen by four doctors all of whom were trained and qualified pediatricians, and they would record on standard form what the child had, and then they were forced, by the nature of the form, to say whether they thought this was bacterial or viral in etiology; and whether this was specifically streptococcal or not. Cultures were obtained before treatment was started. Then the child was given medication or placebo which was pre-determined for him. The moment the child walked in the door, he was automatically assigned a number and the number went with a bottle. No one knew what was in the bottle except the manufacturer. If the child had a streptococcal infection by culture, streptococcal disease, he was removed from the study and given penicillin because this was obviously the thing to do. If the child did not have streptococcal disease, he was continued on either the

placebo medication, which one group received, or on tetracycline which the other group received. Interestingly enough, the incidence of so-called "toxic reactions" was greater with the placebo than it was with the tetracycline itself.

What we were interested in was: Could a clinician tell a viral infection from a bacterial infection by just seeing; the result was he could not. Some people called most things bacterial infections; other people, called most of them viral infections; but generally, the ones who called most things viral infections were usually right, simply because most illnesses *are* viral, but patients whom they firmly believe to have bacterial infections, frequently turned out to be infected with viruses; while those whom they had believed to be viral, frequently turned out streptococcal.

The next thing we said, was, "why don't you start doing white counts?" So, they started doing counts and shifted their interpretation, depending on whether the count was low or high. This did absolutely nothing. They were just as wrong as they had been before! The upshot of all this business was that you couldn't tell what the patient had without a culture. The group that received tetracycline had a statistically higher incidence of secondary infections with involvement of the ears and the sinuses, than the group which did not receive antibiotics. This was more or less what we had anticipated, and is why the study was done as a double blind control. I had very strong prejudices in the direction of not using antibiotics in viral infections. Probably the best protection we have against virulent bacterial infections are the saprophytic bacteria which are always in the nasopharynx. Once they are wiped out by one method or another, the individual becomes more susceptible to other bacterial infections; in fact, he seemingly becomes more susceptible to viral infections also.

I think all of you have seen children who, for one reason or another—partly because they're doctors' children perhaps—are given antibiotics for long periods of time. Every time they get a cold, they go on antibiotics. It's this type of child who has more infections than anybody, and most of these infections are viral rather than bacterial. He also has more complications with his viral infections. Of course, these complications are chiefly bacterial, so antibiotics in a viral infection can probably do harm in two directions: one, it can increase the incidence of bacterial complications; secondly, it can increase the incidence of viral infections

following the first attack of the disease, simply by wiping out the flora and making the individual more susceptible. I think this is all I have to say, and I think the time is ripe for some questions.

DR. JOYNER: I sat through this most of the time with my mouth open (I *had* to open it—my nose being stopped up). I would like to throw discussion open to the floor, but first I would like to ask Dr. Eichenwald one thing: This is the question of the usefulness of a blood count. It disturbed me a little bit. I would certainly agree that differentiation by blood count is not 100% helpful, but I don't think I've ever seen a case I thought was a viral infection, that had a count over 25,000. Now, 10, 12, 14,000 I wouldn't think meant anything—nor do I think a slight shift one way or the other does—but I feel that there is a slight help at times, if you do get a child with a 20 or 25,000 count with 80-85% polys, and another with a 4,500 count who is sitting up playing and having a wonderful time, not overwhelmed by infection—I think the percentages would still be a little bit better on the low count being viral than not.

DR. EICHENWALD: I think you are theoretically correct. The trouble is the percentage of children with respiratory disease and high counts is very small, and in this study, which involved hundreds of children, this accounted for such a small percentage, it was not enough to shift the thing one way or another. If you do get a situation like that, of course, it's significant. The problem is that in most respiratory viruses, with the exception perhaps of influenza, do not really cause a leukopenia. Some do but this also is not usual. The majority of children fall in the range of 12-18,000 WBC, with a mild shift to the left, and this could be anything.

DR. JOYNER: I agree with that. The other thing I'd like to ask right now, we are going through what in the practice of a pediatrician is called telephone advice, and as I mentioned, there's an awful lot of this acute gastritis with vomiting and diarrhea. Now, are those usually due to specific viruses or are they wide groups that happen to land in different intestines at the same time?

DR. EICHENWALD: Generally, I would say in an area like New York City, there are probably several viruses running around. In a smaller area one might anticipate that only a single agent would be responsible. One of the difficulties with disease where you have gastroenteritis and fever is the fact that it is this particular clinical coidition which is most resistant to virologic analysis. The whole

group of diarrheas and gastrointestinal upsets has been very difficult to work with. In the majority of these individuals, one does not obtain viruses. ECHOs and the Coxsackies, while they account for some of the diarrheas, do not seem to play much of a role in the winter and early spring type of situation that we have here.

For years now, people have been trying to infect each other, as well as cats, tissue cultures, and various other things with material from these patients, and this has been unrewarding. Of course, some people would say this is all psychosomatic, but I would say it isn't. This is a specific viral agent, like the agent of hepatitis, or infectious mononeucleosis, that simply hasn't gotten around to being identified.

DR. JOYNER: You *do* think it is a viral agent?

DR. EICHENWALD: Oh yes.

DR. JOYNER: I think it is too. Now, I will take questions from the floor. Dr. Koenig?

DR. KOENIG: I'd like to know when these children with respiratory diseases come into the emergency room, presented with an infected ear, or catarrhal otitis, would you then treat them with antibiotics, or would you still say that this could be a viral infection?

DR. EICHENWALD: Catarrhal otitis we did not treat. If there was any evidence of purulence, then we did. Those were taken out of the study. When you have fluid behind the drum, and even though the fluid may be purulent, you still are unable to identify a bacterial agent in about 20-25%. Playing with statistics, this would mean that the great majority of purulent otitis media is bacterial; but the great majority of non-purulent otitis media—catarrhal otitis media—appears to be viral. The problem one gets into is: in this group, can one protect these children with antibiotics? This I don't know. I would guess the answer would probably be "no". I think they will go on to purulent otitis media in some preordained fashion, that the antibiotic will simply select the organism which will cause the purulent otitis media.

In other words, if you happen to be using tetracycline, you'll end up with a tetracycline resistant staphylococcus perhaps, or with an Aerogenes or something of that nature; if you happen to use penicillin, you might end up with Hemophilus influenza. If you

don't end up with one, you'll get the other because usually these organisms are all present in the nasopharynx.

DR. KOENIG: In our practice you don't very often get a purulent otitis. Most of us treat an otitis media catarrhal with antibiotics so it's very hard to know whether we are over-treating something that doesn't need to be treated at all, or whether you go on using say tetracycline in the hope of stopping it off, and then finding that maybe something stopped it off, either time or the antibiotic.

DR. EICHENWALD: Some day somebody is going to have to do a similar study using only catarrhal otitis media as the test and using a double blind control study.

DR. JOYNER: Wouldn't it be of some aid to compare statistics of the incidence of purulent otitis medias and mastoiditis, now and in the pre-antibiotic era? Certainly in my time, and Dr. Koenig's, and many others here, during an ordinary winter, there were in a ward, anywhere from 5 to 10 mastoids—acute mastoids—at any one time, and there were several people around town here who drove two or three Cadillacs, who did nothing but mastoids. Since then, since we have used antibiotics freely in otitis, it's rare to see an acute mastoid.

DR. EICHENWALD: I think you can effectively treat purulent otitis media.

DR. JOYNER: What do you mean by purulent? When you say purulent, is it draining pus, or is it a fiery red ear with a great deal of pain, and which if you drain it, would probably be pus?

DR. EICHENWALD: Yes, it is that. There have been a number of studies published. In one study recently the investigators introduced a very small needle into the ear-drum, and the fluid was aspirated; it was shown that the majority of these children with painful ears really had a purulent otitis media. I'm not sure whether there is really a decrease in the number of purulent otitis media that one sees. I don't know. I looked for data at our institution, which, of course, are rather biased in various directions, but the proportion of patients who come into our emergency unit each year with purulent otitis media varies a good deal from year to year.

DR. JOYNER: From my own experience I get the impression that we see fewer of them with draining ears. We can't put a needle

through all the infected drums and come back to purulent otitis media as primarily an acute otitis with purulent material, draining from the drums. There have been slightly less of those, and the time that they drain has been cut way down; now, the complications are so few that I have seen only one mastoid in 10 years of practice, and I was sorry for that. I think what we were a little bit at odds about here, was actually somewhat a question of semantics: what Dr. Eichenwald meant by purulent—to us, purulent otitis media means one that has already broken and is draining pus; to him, it would mean an acute ear which may be filled with fluid or not. We can't tell at the time, in other words, acute pain—an acute ear. Any other questions?

VOICE: Dr. Eichenwald, this is a question regarding humanology. In a family where the common respiratory infection is passed from one to the other, and you seem to run into a vicious cycle so that the one who had it first by the end of the month has another—have you ever proved this to be the same virus, or would it be another one?

DR. EICHENWALD: There's considerable evidence that these viruses immunize against themselves; but you see, in this whole discussion I have avoided going into what is usually called a common cold. This is because we find it very difficult to decide what *is* a common cold. Some of these agents cause clinical pictures which are indistinguishable from a common cold. Yet, almost by definition, if a known virus produces a disease, this is no longer a common cold. It's something else.

VOICE: Would you be left with a common cold at the end, or will the common cold not exist as a virus disease?

DR. EICHENWALD: One of the problems is that to work with the common cold is very difficult. I might relate the experience of one group of investigators. They were using volunteers—I forget whom they were using, probably prisoners—and they would spread a little bit of sterile broth in their nose, and these prisoners would be told, "well, in a couple of days, you'll start sneezing" and they developed many symptoms of a cold. These people were isolated from any contact except with the investigator, and he didn't have a cold.

So, while the British work of Dr. Andrews is very interesting, it is difficult to get any really good scientific studies on what the

common cold does consist of, because, since we have to use human beings and since suggestion plays a great role, the problem is very difficult to attack. What they've been doing of course, is to whittle away on this syndrome and find another agent—still another agent, and still another. But there must be some agent which accounts for the true common cold, and which, as we know has a fairly definite incubation period; you get so many attacks each year, and you lose your immunity to it, perhaps over a period of several months. You usually have one at the beginning of the winter, one at the end of the winter, and maybe three a year; this would suggest that there's a fairly definite agent which produces a definite clinical disorder, with a somewhat short immunity duration, making it unique. There is not an unlimited group of agents; otherwise, as pediatricians, where we're exposed to these coughing children all the time, we'd be having a continuous series of these URI's and we don't!

DR. JOYNER: Any other questions?

DR. KOENIG: I have one more question about croup. You said that a great many of these croups were due to viruses. You come in and find a crouping child, with fever usually, sometimes without, —a very severely crouping child—you stick it with streptomycin and penicillin; then certainly, the fever goes down, the croup gradually goes down . . . how are you going to know whether it's viral or not? Again, as a practicing physician, you have to decide then and there whether to treat, or take a chance, and when you have a croup that you're so afraid is going to be something like a dangerous influenzal thing, you hurry up and "stick" a child.

DR. EICHENWALD: Well, I agree you have to treat the children until it's proved one way or the other. By the time proof is at hand the child is well.

DR. KOENIG: Does croup due to a virus last any length of time? How long *does* a croup due to virus last?

DR. EICHENWALD: They're clinically indistinguishable. All croups, no matter what the etiology is, seem to be indistinguishable from each other and this is why I think most people now talk about the croup syndrome. With regard to Hemophilus influenza, there is some disagreement whether this is actually the cause of croup, or simply a secondary invader which converts a possibly minimal inflammation into edema and the whole clinical picture of croup. It

is well established now in the HA-2 situation, that no Hemophilus influenza is necessary—the virus itself will cause severe disease. In fact, a CA virus can kill a patient, no bacteria are necessary; but there may be other agents which cause such minimal amount of edema that the secondary action of Hemophilus influenza is necessary. Also there is a possibility that Hemophilus influenza alone may cause this croup. But from a clinical standpoint, I think one has to treat these children with chemotherapy.

DR. JOYNER: Any other questions?

VOICE: How about a child with just a red throat? Let's say we can't distinguish viral from bacterial infection, would we do more harm by treating all these children with antibiotics; or will we do more harm by not treating them, and say, missing a streptococcal infection?

DR. EICHENWALD: If you treat, you've got to do two things: you've got to treat with penicillin, and you've got to treat for 10 days. If you want to treat—if you take the attitude you want to prevent streptococcal consequences, and that's the reason for treating sore throats—then, you have to treat every one of them in this way, with penicillin, knowing that you're going to be treating approximately 9 viral infections, for every one streptococcal infection. This is true whether there is exudate or not, by the way, because non-streptococcal exudative tonsilitis is more common than streptococcal infections.

VOICE: You can also have a strep throat without exudate too, can't you?

DR. EICHENWALD: Certainly.

DR. KOENIG: I think the reason we treat, if we treat at all, is because we try to avoid otitis and its complications.

DR. JOYNER: Yes Doctor?

VOICE: In your opinion, would it be worth reimmunizing medical hospital staffs and others with the influenza virus vaccines right now?

DR. EICHENWALD: I would say no. I think medical personnel has most certainly been exposed to Asian flu and most certainly has immunity. As I indicated in my talk 70% of the general population in the New York area has immunity, and I would say 99.8%

of the medical profession must have immunity. The vaccine, as you know, causes reactions on lots of people. I don't think it's worth using unless we have a real, definite indication that something is happening.

VOICE: But there have been cases. There are two here in the hospital now, of possible influenza or virus infection, who came from the West Coast by plane into New York.

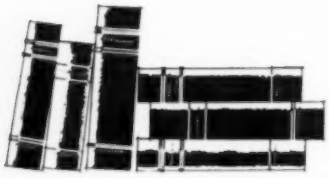
DR. EICHENWALD: In 9 other States there are proved cases of A2, but these are in areas where in the last two years, there has not been much influenza.

VOICE: Right.

DR. JOYNER: Dr. Eichenwald, I'd like to ask one other question and close the discussion. With the exception of the specific pandemic type of flu vaccine, do you know of any so-called cold or upper respiratory vaccine that does any good?

DR. EICHENWALD: No I do not.

DR. JOYNER: I want to thank you very much for this most interesting and instructive talk.



. . . Books

Edited by

MICHAEL A. BRESCIA, M.D.

THE MOTHER-CHILD INTERACTION IN PSYCHOSOMATIC DISORDERS: By Ann M. Garner and Charles Wenar. Cloth. 290 pp. Price $6.00. Urbana: University of Illinois, 1959.

Drs. Ann Garner and Charles Wenar, formerly psychologists with the Department of Psychiatry of the University of Illinois College of Medicine, were interested in deriving a testable hypothesis about the etiology of psychosomatic disorders in children. An intensive research project, which integrated the findings of psychologists, pediatricians, psychiatrists, social workers, and others, was set up, to test the central hypothesis that mothers of children with psychosomatic illnesses, such as asthma, colitis, etc., lack "motherliness" in caring for their infants during the crucial first year of life. Although the authors were chiefly responsible for designing the experiment, and evaluating the results, many persons and institutions contributed to the theoretical and practical aspects of this study. The investigation was supported by a research grant from the National Institute of Mental Health. Part I concerns itself with procedures, findings and conclusions, while Part II is devoted to the details of methodology. The authors were not unaware of the shortcomings inherent in an investigation which is essentially experimental, however, they felt that they had preserved the clinical aspects of their undertaking, while not losing sight of the methodology and statistics.

As basic in the development of psychosomatic susceptability, the authors hypothesize a particular and unique disturbance between mother and infant. Neither neglect nor overt rejection are involved. The supposition here is, that the mother-child interaction is mutually frustrating, since the mother is not capable of meeting the needs of the infant smoothly and effectively. The present study owes the major part of its theoretical basis to the work of Margaret W. Gerard and her psychoanalytic approach to the subject. Emphasis is also given in this present research, to Roy R. Grinker's theory of the organism's response to stress due to lack of gratification. It is significant to note that the authors differ from Franz Alex-

ander, who stresses the specificity of conflict underlying psychosomatic ills; and also the view that psychosomatic symptomatology develops within an essentially neurotic personality. The disorders dealt with in this study resemble more that of a psychotic, than a neurotic organization.

A variety of considerations determined the final selection of the population from which the conclusions have been drawn. Random samples of psychosomatic, neurotic, and physically ill patients were selected. There were seventy-eight children in all, aged six to twelve, equated for intelligence, sex, race, socio-economic status and family constellation. By retrospective and reconstructive techniques, the authors were able to study early patterns of mothering and were able to epitomize the "psychosomatic mothers" as follows: Ambitious, controlling women who find the actual caretaking of the infant unrewarding or disagreeable; however, they are so irresistibly drawn to this ungratifying activity, that they became entangled in a mutually frustrating relationship. The hypothesized effects upon the infant are that he does not receive continuous protection from distress, and perpetuates a pattern of erratic response to stress. Because of his first interpersonal environment, he associates intimacy with distress. ELEANOR ROTHENBERG, M.A.

PEDIATRIC NEUROLOGY: By Stanley S. Lamm, M.D. Pages 495, cloth. Landsberger Medical Books, Inc. 51 East 42nd St., New York, N. Y. 1959. Price $12.00.

This is an excellent book for the beginning study of the nervous system. The style is clear cut, simple and to the point. Verbosity and triple-plated words have been omitted. This book is a pleasure for the busy pediatrician to read.

Doctor Lamm's classifications and groupings of neurological conditions have been so systematically and skillfully arranged that confusion in reading and interpreting the material is kept at a minimum.

The chapter on "Miscellaneous" which includes brain injured children, aphasia, stuttering, disorders of hearing and many other problems will give a fine working vocabulary to the average pediatrician who is confronted with an habilitation problem.

Here is a reference book that any doctor working with children should have in his library. The chapter headings are concise and so is the material that is covered in each chapter.

Thank you, Doctor Lamm, for producing a medical reference book on pediatric neurology that reads like a fascinating novel with its wealth of up to the minute material.

CATHERINE E. SPEARS, M.D.

DIE HERZINSUFFIZIENZ IN DER PRAXIS, by Kurt Block, M.D. Ph.D. 216 pp. Georg Thieme Verlag Stuttgart 1958.

This book attempts to teach the practitioner how to utilize clinically the newer knowledge in cardiology. An extensive clinical experience combined with a thorough knowledge of the literature qualify the author to undertake such a project.

The book consists of a sketchy description of the anatomy, physiology, pathology, biochemistry, symptomatology, diagnostic methods, and differential diagnosis relating to cardiology. The amount and breadth of material presented is surprisingly large. Its effectiveness, however, is reduced by its brevity.

The section on therapy is more detailed. Digitalis therapy is well presented; the author's experience has made him a master of this difficult subject. Practically nothing is said of anti-coagulation therapy. Quinidine and procaine amide are barely mentioned, while Camphor injections are still recommended.

Had the author been more discriminating in his choice of subjects and had he written more about less, the result would have been more informative. As it now stands, a reader familiar with German can obtain from it a bird's-eye view of clinical cardiology.

A. I. SCHAFFER, M.D

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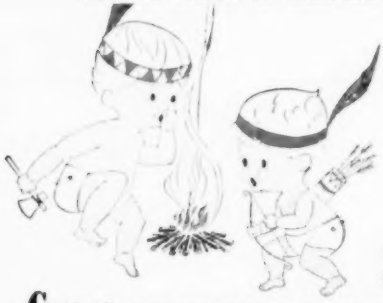

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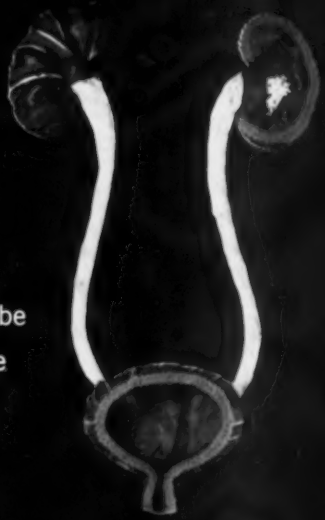

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